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High Yield Endoselective Heterocycloadditions involving Benzylidenepyruvic Esters as the Heterodiene and an Alkoxystyrene as the Dienophile

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Abstract : The benzylidenepyruvic esters **6**, **10a-d** and **11** smoothly reacted with the alkoxystyrenes **12** and **13** in refluxing hexane or toluene and in the presence of catalytic amounts of Eu(fod)3, thus selectively leading to the *endo* adducts **14-21** in high yields. This represents the first examples of an efficient heterocycloaddition of styrene derivatives without using the high pressure technique. The above adducts are potential intermediates for sugiresinol **7** and related tetrahydropyran neolignans.

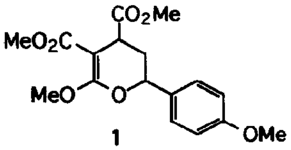
There are relatively few known cases of inverse type Diels-Alder heterocycloadditions of α,β-ethylenic carbonyl compounds with styrene derivatives. Indeed, this particular reaction is only illustrated by isolated examples scattered in the literature. Thus, as early as 1951, Smith and coworkers[1] treated acrolein with α-methylstyrene at 180 °C and obtained the corresponding 2-methyl-2-phenyldihydropyran in 23 % conversion rate. Using simple analogues of acrolein as the heterodiene also gave poor yields. On the other hand, 1,1-diphenylethylene reacted with arylidenemalonaldehydes at room temperature in the presence of zinc iodide as a catalyst and afforded the corresponding substituted dihydropyran-3-carboxaldehydes in moderate yields.[2] A 2-cyanodihydropyran was similarly obtained upon reaction of styrene with isopropylideneacetyl cyanide in the presence of aluminium chloride at room temperature (41 % yield).[3] The reaction of p-methoxystyrene with trimethyl ethylenetricarboxylate at 70 °C or 116 °C in various solvents gave the cycloadduct **1** in yields below 30 %.[4] Somewhat better results were observed when using dimethyl cyanofumarate as the heterodiene. In their studies related to the synthesis of C-aryl glucosides, Schmidt and coworkers[5] found that reaction of the heterodiene **2a** with 4-methoxystyrene under high pressure conditions (5,2 kbar at 60 °C), regio- and *endo*-specifically afforded the adduct **3** in 57 % yied. Similarly from 3,4-dimethoxystyrene and **2b** the dihydropyran **4** was obtained with a moderate stereofacial selectivity (3:1). More recently, it was found that heating 2-formyl-4,4-dimethylcyclohexadienone with 4-methoxy, 3,4-dimethoxy and 3,4,5-trimethoxystyrene yielded the corresponding benzopyranones **5** , the *endo* addition being favoured.[6]

So far as we know, no Diels-Alder heterocyclisations involving styrene derivatives were carried out using lanthanide complexes,[7] although the latter proved to be very efficient catalysts for similar reactions.[8] Indeed we obtained very good results in the Eu(fod)3-catalyzed heterocycloadditions of methyl benzylidenepyruvate **6** with chiral vinyl ethers.[9]

With these facts in mind, we undertook a study of the lanthanide-catalyzed heterocycloaddition of various arylidenepyruvic esters with substituted styrene derivatives, with the ultimate aim of synthesizing neolignans of the sequirin series, such as sugiresinol **7**.

Synthesis of arylidenepyruvic esters

Upon treatment with hot methanol in the presence of hydrochloric acid, p-nitrobenzaldehyde afforded the dimethyl acetal **8a**.[10] 4-Methoxybenzaldehyde, piperonal and 3,4,5-trimethoxybenzaldehyde were each treated with trimethyl orthoformate in the presence of montmorillonite K10 in dry methanol for 2-3 days at room temperature,[11] thus giving the corresponding dimethyl acetals **8b**, **c** and **d**,[10] respectively, and in good yields. The latter were next condensed with the trimethylsilyl ether **9** of methyl pyruvate according to a known general procedure.[12] Thus each acetal **8a-d** (1.1 eq.) was reacted with the enol ether **9** (1 eq.) in dry CH_2Cl_2 and in the presence of $BF_3.Et_2O$ (1.1 eq.) at -78 °C for 3 h under argon. After treatment of the crude reaction product with silica gel in toluene overnight under reflux, the corresponding methyl arylidenepyruvates **10a-d**[10] were isolated in 74-95 % yields. Finally, methyl 4-methoxybenzylidenepyruvate **10b** was treated with bromine in CCl_4 in the presence of pyridine for 1 h at 10 °C, thus affording the vinylic bromide **Z-11**[10] as a



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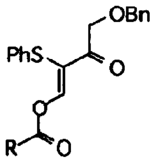
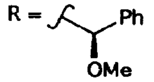
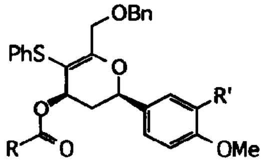


2a R = Me

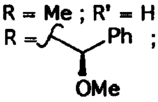
2b R =



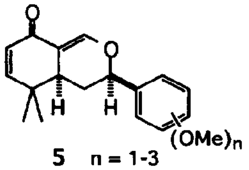


3 R = Me ; R' = H

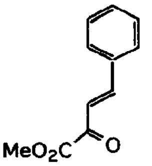
4 R =



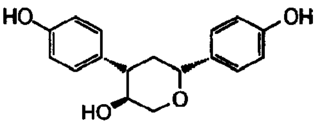
; R' = MeO



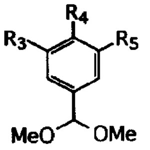
5 n = 1-3



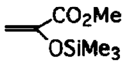
6



7

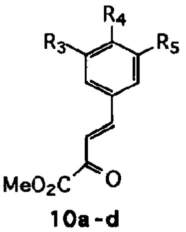


8a-d

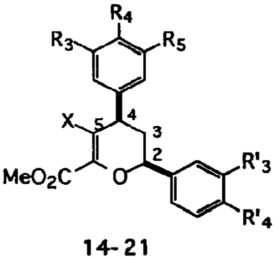


9

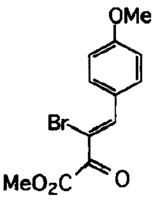
a $R_4 = NO_2$; $R_3 = R_5 = H$
b $R_4 = MeO$; $R_3 = R_5 = H$
c $R_3, R_4 = -OCH_2-O$; $R_5 = H$
d $R_3 = R_4 = R_5 = MeO$



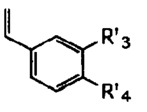
10a-d



14-21



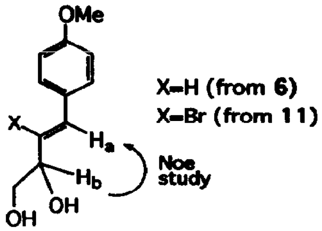
11



12 $R'_3 = H$; $R'_4 = MeO$
13 $R'_3, R'_4 = -OCH_2O-$

14 X = H ; $R_3 = R_4 = R_5 = R'_3 = H$; $R'_4 = MeO$
15 X = H ; $R_3 = R_5 = R'_3 = H$; $R_4 = R'_4 = MeO$
16 X = Br ; $R_3 = R_5 = R'_3 = H$; $R_4 = R'_4 = MeO$
17 X = H ; $R_3 = R_5 = R'_3 = H$; $R_4 = NO_2$; $R'_4 = MeO$
18 X = H ; $R_3, R_4 = OCH_2O$; $R'_4 = MeO$; $R'_3 = R_5 = H$
19 X = H ; $R_4 = MeO$; $R'_3, R'_4 = OCH_2O$; $R_3 = R_5 = H$
20 X = H ; $R_3, R_4 = R'_3, R'_4 = OCH_2O$; R_5=H
21 X = H ; $R_3 = R_4 = R_5 = MeO$; $R'_3, R'_4 = OCH_2O$

single, sharp-melting compound. Stereochemical assignment of the double bond of compound **11** was achieved by NMR studies of the glycols obtained by $NaBH_4$ reduction of E-**6** and its bromo analogue **11**.[13] NOE difference measurements showed approximately the same enhancement between H_a and H_b in both cases : indeed, 6 % and 8 % enhancements were observed for the glycols deriving from E-**6** and **11**, respectively. These facts confirm the Z configuration of the starting bromoalkene **11**.



Heterocycloaddition reactions

4-Methoxystyrene **12** is commercially available. 3,4-Methylenedioxystyrene **13**[10] was obtained by reaction of piperonal with methyl triphenylphosphonium bromide in the presence of potassium carbonate in refluxing diglyme for 24 h. In the next step, each heterodiene **6**, **10a-d** and **11** was treated with 1.2 eq. of one of the above alkoxystyrenes **12** or **13** in refluxing hexane or toluene for 2 to 11 days and in the presence of a 5 % molar amount of the lanthanide catalyst $Eu(fod)_3$. Under these conditions, the heterocycloaddition reaction proceeded smoothly and afforded high yields of the corresponding adducts **14-21**,[10] in which the *endo* diastereomer is largely predominant (>92 % in all cases and >97 % when the dienophile was p-methoxystyrene **12**) (see Table). This high *endo* selectivity was evidenced by examination of the 400 MHz ^1H NMR spectra of the adducts **14-21** which displayed common features. In all cases, both H_3 protons are distinct. The more shielded H_3 proton is *pseudo*-axial and appears as a multiplet having three large coupling constants with $H_{3\text{-eq}}$, H_2 and H_4. The lesser shielded H_3 proton is *pseudo*-equatorial and shows up as a multiplet having four coupling constants with $H_{3\text{-ax}}$ (large), H_4 (middling), H_2 and H_5 (small). $H_{3\text{-ax}}$ has two vicinal coupling constants, J = 11-11.5 Hz, which indicates that both vicinal protons H_2 and H_4 are *pseudo*-axial. Therefore, the aryl substituents at C_2 and C_4 of the dihydropyran ring of the adducts **14-21** are *cis-pseudo*-equatorial, which corresponds to an *endo* cycloaddition reaction. NOE measurements carried out with the dimethoxy adduct **15** confirmed the relative 2,4-*cis*-di-equatorial configuration in this particular case.[13,14] In the cases where the minor *exo* adduct is apparent in the ^1H NMR spectrum, the conformation is *pseudo*-equatorial for the C_2 aryl substituent and *pseudo*-axial for the C_4 aryl substituent.This unexpected

X	R_3	R_4	R_5	R'_3	R'_4	Heterodiene	Styrene		Adducts		
									Experimental conditions a)	Yield (%) b)	Endo/Exo ratio
H	H	H	H	H	MeO	**6**	**12**	**14**	Hex (60°C) 2d.	97	>97/3
"	"	MeO	"	"	"	**10b**	"	**15**	" 3d.	98(83) c)	"
Br	"	"	"	"	"	**11**	"	**16**	" 7d.	83	"
H	"	NO_2	"	"	"	**10a**	"	**17**	" 2d.	74	"
"	$O\text{-}CH_2\text{-}O$		"	"	"	**10c**	"	**18**	" 6d.	96	"
"	H	MeO	"	$O\text{-}CH_2\text{-}O$		**10b**	**13**	**19**	" 7d.	90	96/4
"	$O\text{-}CH_2\text{-}O$		"	"		**10c**	"	**20**	Tol (110°C) 6d.	95	92/8
"	MeO	MeO	MeO	"		**10d**	"	**21**	" 11d.	77	95/5

a) Hex = hexane, Tol = toluene, d = days b) Yields of purified product c) The value in brackets refers to crystallized product.

Table : Heterocycloadditions of arylidenepyruvic esters (**6**, **10a-d**,**11**) with styrenes (**12**, **13**) catalyzed by $Eu(fod)_3$.

conformation, which may be due to allylic interaction, is ascertained by the following coupling constants : $J_{H2\text{-}H3ax}$ = 9 Hz, $J_{H2\text{-}H3eq}$ = 2 Hz and $J_{H4\text{-}H5}$ = 5 Hz. On the other hand, it should be emphasized that the *endo* bromoadduct **16** has a *cis*-2,4-di-*pseudo*-equatorial conformation developing a $A^{(1,2)}$ allylic strain between the vinylic bromine atom and the C4 aryl substituent.[15] Interestingly, this interaction is more favourable than the predictable 2,4-diaxal interaction between both aryl substituents in the other possible conformation of the adduct **16**.

As expected, the results displayed in the Table show that the more electrodeficient the heterodiene is, the more reactive it is. Thus, the most reactive heterodienes are methyl benzylidenepyruvate **6** and its p-nitrophenyl analogue **10a**. As a dienophile, p-methoxystyrene **12** is more reactive than its 3,4-methylenedioxy analogue **13**. As a matter of comparison, the reaction between methyl benzylidenepyruvate **6** and p-methoxystyrene **12** was brought to completion within two days at 60 °C, whereas the same reaction between methyl 3,4,5-trimethoxybenzylidenepyruvate **10d** and 3,4-methylenedioxystyrene **13** required eleven days at 110 °C (see Table).

Conclusion

By combining the activating effect of a methoxycarbonyl group at position 2 of the heterodiene with a catalysis by the lanthanide complex Eu(fod)3, the heterocycloaddition afforded excellent yields of the *cis*-2,4-diaryl-2,3-dihydropyrans (4H) **14-21** with complete or very high *endo* selectivity. These results represent the first examples of an efficient heterocycloaddition of styrene derivatives without using the high-pressure technique. The dihydropyrans **14-21** are potentially useful intermediates for the syntheses of neolignans of the sugiresinol **7** series.

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10. Physical properties and yields of compounds : [16] **8a**, oil, 45 % (crude) ; **8b**, oil, 68 % (crude) ; **8c**, oil, 99 % (crude) ; **8d**, oil, 87 % (crude) ; **10a**, m.p. 184 °C (Tol/Pet. Ether), 74 % ; **10b**, m.p. 109 °C (AcOEt),85 % ; **10c**, m.p. 141 °C (AcOEt), 85 % ; **10d**, m.p. 112 °C (AcOEt), 95 % ; **11**, m.p. 80 °C (AcOEt/Pet.Ether), 74 % ; **13**, oil, 33 %. Physical properties of adducts : **14**, m.p. 116 °C (Et_2O) ; **15**, m.p. 92.5 °C (AcOEt/Pet. Ether) ; **16**, m.p. 103 °C (AcOEt/Pet. Ether) ; **17**, m.p. 135.5 °C (Tol/Pet. Ether) ; **18**, oil ; **19**, m.p. 85 °C (Et_2O) ; **20**, oil ; **21**, m.p. 126 °C (Et_2O/Pet. Ether).
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14. Characteristic ^{1}H NMR (400 MHz) data of the adduct **15** (in $CDCl_3$), δ (ppm) : 5.05 (dd, J = 11.3 Hz and 1.2 Hz) $H_{2\text{-}ax}$; 1.95 (dt, J = 13.8, 11.4 and 11.3 Hz) $H_{3\text{-}ax}$; 2.32 (ddt, J = 13.8, 6.4, 1.5 and 1.5 Hz) $H_{3\text{-}eq}$; 3.85 (ddd, J hidden) $H_{4\text{-}ax}$; 6.20 (t, J = 1.8 Hz) H_5.
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